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Predictive Value of Platelet-Related Measures in Patients with Hepatocellular Carcinoma

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Abstract

Background: Increasing numbers of studies reported platelet (PLT)- related measures could play a creative role in many malignancies, while the prognostic impact of these measures in hepatocellular carcinoma (HCC) remains limited and controversial. It is worth exploring the predictive value of PLT-related measures in HCC. **Methods:** A total of 279 HCC patients with hepatectomy were analyzed in the retrospective cohort study. The optimal cut-off points of these PLT-related indices were obtained by the receiver operating characteristic (ROC) curve. The associations of these indices with clinical characteristics and overall survival (OS) were evaluated by Kaplan–Meier curves and Cox proportional hazards models. **Results:** High PLT count and low prognostic nutritional index (low-PNI) were significantly associated with larger tumor size. The low gamma-glutamyl transpeptidase-to-platelet ratio (low-GPR) group was inclined to more hepatitis infections. Survival curves indicated that preoperative high-PLT, low-GPR, and low-PNI had a worse prognosis after surgery in the cohort. In addition, PLT$\geq 220 \times 10^9$/L (HR, 2.274; 95% CI, 1.061-4.876; $P = .035$), PNI$\geq$51.9 (HR, 0.503; 95% CI, 0.265-0.954; $P = .035$), and GPR$\geq$0.2 (HR, 0.432; 95% CI, 0.204-0.912; $P = .028$) were identified as independent prognostic factors for survival outcomes in the multivariable analysis. **Conclusion:** High-PLT, low-GPR, and low-PNI as the preoperative predictors were associated with poor OS in HCC patients with hepatectomy. Our data reveal that they could be simple, easily obtained, and effective predictors for evaluation of survival outcomes in patients.

Keywords

hepatocellular carcinoma, blood platelets, prognosis, gamma-glutamyl transpeptidase-to-platelet ratio, prognostic nutritional index

Abbreviations

APPR, alkaline phosphatase-to-platelet ratio; GPR, gamma-glutamyl transpeptidase-to-platelet ratio; HCC, hepatocellular carcinoma; MPV, mean platelet volume; OS, overall survival; PDW, platelet distribution width; PLR, platelet to lymphocyte ratio; PLT, platelet; PNI, prognostic nutritional index; ROC, receiver operating characteristic.

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Introduction

Hepatocellular carcinoma (HCC) is one of the deadliest diseases, ranking as the sixth most common cancer and the fourth leading cause of tumor-related death.[1] The mortality rates have increased over recent decades in many countries, especially in China, which accounts for over half of new cases and deaths worldwide.[2] Recently, some improvements are achieved owing to the progress of the treatments, such as surgical resection, liver transplantation, and transarterial chemoembolization.[3] However, the 5-year cause-specific survival rate of HCC remains less than 20% for all stages combined diagnosed, at a low level in human cancers.[4] The main reasons for the poor outcome include difficulties in early diagnosis, rapid progression of advanced liver cancer, and deficiency in practical prognostic assessment.[5] Thus, risk stratification is critical to improving overall survival (OS), particularly in high-risk HCC patients.

Platelet (PLT) characteristics are important inflammatory parameters, and platelets are also associated with the development, invasion, metastasis, and recurrence of cancer.[6] Some platelet-based measures such as platelet count, mean platelet volume (MPV), platelet distribution width (PDW), and platelet-to-lymphocyte ratio (PLR) were significantly associated with the prognosis of HCC patients,[7,8] although their roles in predicting survival outcomes are still controversial. Taking platelet count as an example, some studies demonstrated that thrombocytopenia was strongly associated with improved survival,[9] while others showed that preoperative thrombocytopenia was a negative predictor of OS.[10] Besides, some new hematologic markers combining liver function and platelet function have been paid considerable attention. Gamma-glutamyl transpeptidase-to-platelet ratio (GPR) and alkaline phosphatase-to-platelet ratio (APPR) could be auxiliary diagnostic indicators to improve early detection of HCC.[11]

In the study, the prognostic significance of these platelet-related indices was systematically evaluated for predicting the survival of HCC patients after surgical resection.

Methods

Study Population and Study Design

A total of 337 HCC patients with hepatectomy were recruited consecutively in the cohort study from May 2013 to January 2014. HCC patients with diabetes were not included in this cohort because diabetes is associated with poor OS and disease-free survival per se, and it has a significant impact on platelet counts and platelet-based parameters.[12] Patients were included if meeting all the following criteria: (1) pathological diagnosis of HCC without distant metastasis; (2) complete clinical, pathological and surgical data; and (3) no previous anticancer treatment with chemotherapy and radiofrequency ablation before surgery; Simultaneously, patients were excluded if not meeting any of the above criteria from analyses to account for bias. Ultimately, 279 patients (median age 51, range:19-81years) were included and analyzed in the retrospective study. The Medical Ethics Committee of our institute approved this study. The written informed consent following the Declaration of Helsinki was provided to all patients and we have de-identified all patient details. The reporting of this study conforms to STROBE guidelines.[13]

Follow-up

All the participants were followed-up by outpatient visits. The routine reexaminations included liver function, alpha-fetoprotein (AFP), abdominal ultrasound, and enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Overall survival (OS) was defined as the months from the date of surgery to the time of death or last follow-up. The follow-up was ended in September 2017 for this cohort.

Data Acquisition and Definitions

The clinical features, including age, hepatitis, cirrhosis, antiviral therapy, tumor size, tumor markers (such as AFP, CEA, and CA199), tumor numbers, microvascular invasion, etc., were obtained from the medical records of the patients.

Hematologic and liver function parameters, including platelet count, lymphocyte count, serum gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), and albumin levels were obtained within three days before surgery. The data from these parameters were used to calculate platelet-related indices: platelet to lymphocytes ratio (PLR), GGT to platelet ratio (GPR), and ALP to platelet ratio (APPR). Also, The prognostic nutritional index (PNI) was calculated with the formula: serum albumin level (g/L) + 5 × total lymphocyte count (10^9/L), as previously reported.[14] Coagulation markers, prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen (FIB) were also analyzed in the cohort.

Statistical Analysis

All statistical analyses were performed using SPSS statistics 22 (IBM SPSS, Inc., USA). Continuous data were expressed as mean (*SD*) or median (interquartile range), and the Student's *t*-test or the nonparametric Mann–Whitney test were used for statistical analyses. Categorical variables were presented as numbers (n) and proportions (%) of patients. The chi-square tests or Fisher's exact tests were used for statistical analyses. The correlation between the platelet-related parameters and clinical features was assessed using the Pearson's or Spearman's correlation coefficients. Receiver operating characteristic (ROC) analyses were performed to determine the optimal cut-off point for these parameters. Cumulative survival rates were estimated by the Kaplan-Meier method. Univariable and multivariable Cox regression analyses were performed to identify prognostic factors associated with OS. Propensity score matching analysis in a 1:2 ratio was employed to reduce the confounding effect of tumor-related factors affecting prognostic survival. A P-value < .05 was considered statistically significant.

Table 1. Comparison of Clinical Characteristics of Patients Stratified by the Level of Different in Platelet-Related Measures.

		PLT			GPR			PNI		
Categories	Total (n = 279)	<220 (n = 244)	≥220 (n = 35)	*P* value	<0.2 (n = 35)	≥0.2 (n = 242)	*P* value	<51.9 (n = 187)	≥51.9 (n = 91)	*P* value
Age (years)	51.1 ± 11.6	51.3 ± 11.3	49.7 ± 13.3	.452	48.1 ± 13.9	51.5 ± 11.2	.110	51.2 ± 11.0	50.8 ± 12.8	.798
Etiology, n (%)										
Hepatitis	225 (80.6)	200 (82.0)	25 (71.4)	.126	33 (94.3)	190 (78.5)	.030*	155 (82.9)	69 (75.8)	.136
Crrhosis	259 (92.8)	228 (93.4)	31 (88.6)	.293	32 (91.4)	226 (93.4)	.718	177 (94.7)	81 (89.0)	.088
Antiviral therapy	60 (21.5)	57 (23.4)	3 (8.6)	.046*	6 (17.1)	54 (22.1)	.502	39 (20.9)	21 (23.1)	.673
Tumor Markers										
AFP≥100ug/L, n (%)	131 (47.0)	109 (44.7)	22 (62.9)	.044*	15 (42.9)	114 (47.1)	.712	94 (50.3)	36 (39.6)	.093
CA199 ≥ 40 U/mL, n (%)	47 (16.8)	40 (16.4)	7 (20.0)	.594	1 (2.9)	46 (19.0)	.017*	36 (19.3)	11 (12.1)	.135
CEA (ug/L)	2.4 (1.5,3.5)	2.4 (1.6, 3.5)	2.2 (1.1, 3.3)	.307	2.4 (1.5, 3.8)	2.4 (1.6, 3.4)	.965	2.4 (1.6, 3.5)	2.4 (1.4, 3.3)	.342
Tumor Factors										
Tumor size (cm)	7.6 ± 4.2	7.3 ± 4.0	10.1 ± 4.4	.0002*	6.5 ± 3.6	7.7 ± 4.1	.089	8.0 ± 4.3	6.8 ± 3.6	.017*
Multiple tumors, n (%)	50 (17.9)	42 (17.2)	8 (22.9)	.416	1 (2.9)	48 (19.8)	.014*	37 (19.8)	12 (13.2)	.175
Microvascular invasion	106 (38.0)	92 (37.7)	14 (40.0)	.807	6 (17.1)	99 (40.9)	.006*	79 (42.2)	26 (28.9)	.032*
Liver Biochemistry										
GGT (U/L)	77 (44.0,146.5)	69 (43.0,133.0)	90 (60.5,204.5)	.036*	27 (20.8,31.0)	90 (51.8,160.3)	< .0001*	85 (44.8,151.0)	65 (40.3,122.0)	.121
ALP (U/L)	84 (67.0,102.8)	84 (66.0,100.0)	84 (70.5,134.0)	.133	69 (60.5,84.0)	86 (69.8,107.8)	.0002*	88 (72.0,107.8)	77 (58.8,97.3)	.001*
Serum total bilirubin (umol/L)	15.0 ± 5.9	15.0 ± 5.9	14.5 ± 5.6	.613	14.3 ± 4.7	15.0 ± 6.0	.499	15.3 ± 6.1	14.3 ± 5.3	.200
Serum albumin (g/L)	41.7 ± 3.5	41.7 ± 3.4	41.9 ± 4.1	.672	42.4 ± 3.4	41.6 ± 3.4	.165	40.2 ± 2.7	44.8 ± 2.7	< .0001*
Laboratory results										
WBC (*10^9/L)	5.6 ± 1.8	5.3 ± 1.6	7.3 ± 2.3	< .0001*	5.8 ± 2.0	5.5 ± 1.8	.364	5.2 ± 1.7	6.3 ± 1.9	< .0001*
LYM (*10^9/L)	1.6 ± .6	1.6 ± 0.6	1.9 ± 0.7	.004*	1.7 ± 0.5	1.6 ± 0.6	.391	1.4 ± 0.4	2.1 ± 0.6	< .0001*
PLT (*10^9/L)	156.7 ± 62.6				190.7 ± 72.8	150.7 ± 58.6	.0003*	147.8 ± 59.8	173.3 ± 63.3	.001*
MPV (fL)	11.6 ± 1.1	11.7 ± 1.0	10.8 ± 1.1	< 0.0001*	11.1 ± 1.0	11.6 ± 1.1	.006*	11.6 ± 1.2	11.4 ± 0.9	.244
Inflammatory indices										
PLR	94 (73.3,129.4)	91 (69.8,120.1)	159 (119.4,188.0)	< .0001*	109 (90.4,133.8)	93 (69.8,127.2)	.018*	103 (79.1,136.9)	81 (61.7,106.8)	< .0001*
PNI	49.6 ± 5.7	49.3 ± 5.7	51.4 ± 5.5	.046*	49.7 ± 9.4	49.5 ± 4.9	.903			
GPR	0.54 (0.28,1.05)	0.56 (0.30, 1.06)	0.39 (0.21, 0.79)	.033*				0.58 (0.30, 1.21)	0.42 (0.24, 0.81)	.008*

Data are presented as mean ± *SD* or median (IQR).

Abbreviations: AFP: α-fetoprotein; ALP: alkaline phosphatase; CEA: carcinoembryonic antigen; GGT: gamma-glutamyl transpeptidase;GPR: gamma-glutamyl transpeptidase-to-platelet ratio; LYM:, lymphocyte; MPV: mean platelet volume; PLT: platele ; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; WBC: white blood cell.

**P* value <.05 was considered significant.

Table 2. Correlation of Hematologic Parameters with the Main Characteristics of Patients.

	PLT		GPR		PNI	
Variables	r	*P* value	r	*P* value	r	*P* value
Antiviral therapy	−0.163	.006	−0.043	.479	−0.020	.736
Tumor size	0.290	< .0001*	0.196	.001*	−0.222	.0002*
Microvascular invasion	−0.048	.423	0.254	< .0001*	−0.159	.008
Serum total bilirubin	−0.129	.032	0.094	.119	0.008	.899
ALP	0.120	.046	0.414	< .0001*	−0.070	.250
WBC	0.609	< .0001*	−0.163	.006	0.392	< .0001*
NEU	0.536	< .0001*	−0.112	.063	0.176	.003*
LYM	0.384	< .0001*	−0.231	.0001*	0.679	< .0001*
MPV	−0.485	< .0001*	0.190	.002*	−0.125	.041
PDW	−0.491	< .0001*	0.190	.002*	−0.078	.200
PLR	0.576	< .0001*	−0.146	.015	−0.320	< .0001*

Abbreviations: ALP: alkaline phosphatase; GPR: gamma-glutamyl transpeptidase-to-platelet ratio; LYM: lymphocyte; MPV: mean platelet volume; NEU: neutrophil; PLT: platelet; PDW: platelet distribution width; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; r: correlation coefficient; WBC: white blood cell.
**P* value <.0045 was considered significant (after Bonferroni correction).

Results

Association of Platelet-Related Measures with Clinical Characteristics

A total of 279 from 337 HCC patients received surgical resection were enrolled in this cohort with the exclusion of 2 patients with previous treatment, 3 with distant metastasis, 32 with lost to follow-up, and 21 with missing preoperative hematologic parameters data. The baseline clinical characteristics of patients were summarized in Table 1. A total of 225 patients (80.6%) had viral hepatitis, and 259 (92.8%) developed cirrhosis. Increased AFP levels (≥100 μg/L) were observed in 131 patients (47.0%), and the mean diameter of the greatest tumor was 7.6 cm.

Patients were divided into two groups, the low-PLT and high-PLT group to observe the association of platelet count with the clinicopathologic features. The cut-off point was determined for PLT (220×10^9/L) by the ROC plot. As shown in Tables 1 and 2, a significantly larger diameter of the tumor, more white blood cell (WBC) count, higher PLR and PNI were observed in patients with high-PLT. PLT count was also significantly correlated with WBC count (r = 0.609, $P <$ .0001) and PLR (r = 0.576, $P <$ .0001), and negatively correlated with MPV (r = -0.485, $P <$ .0001) and PDW (r = -0.491, $P <$ .0001).

Patients were also divided into two groups based on the GPR value (cut-off value is 0.2) by the ROC plot. The low-GPR (<0.2) group had a higher rate of hepatitis virus infection, higher PLT count, and higher PLR compared to those of the high-GPR (≥0.2) group. Also, GPR was significantly and positively correlated with ALP (r = 0.414, $P <$ .0001).

Patients were further divided into two groups by PNI with a cut-off value of 51.9 through the ROC plot. A total of 187 patients were categorized as low-PNI (<51.9) and the remaining patients as high-PNI (≥51.9). The low-PNI patients showed larger tumor size, higher ALP, and higher PLR, but lower serum albumin, WBC count, and PLT count. In addition, PNI was significantly correlated with WBC count (r = 0.392, $P <$ .0001), lymphocyte count (r = 0.679, $P <$ .0001), and PLR (r = -0.320, $P <$ .0001).

Identification of Preoperative Factors for Predicting the Survival of HCC Patients with Surgery

The median overall survival of all patients was 46.0 months, and 71.7% of patients remained alive during the follow-up period. The association between preoperative factors and overall survival was analyzed in Table 3. Univariable analysis showed that the following preoperative factors were significantly negatively correlated with OS: age≥58 years ($P =$ .023), hepatitis ($P =$ .039), PLT≥220×10^9/L ($P =$ .001), PDW<12.8% ($P =$ .049), PLR≥116 ($P =$ 0.016), PNI<51.9 ($P =$ .026), GPR<0.2 ($P =$ .014), and APPR<0.55 ($P =$ .042). Multivariable analysis by adjusting for all the confounding factors indicated that these factors significantly impacted OS during the follow-up period, they are: age≥58 years (HR, 2.227, 95% CI, 1.347-3.850, $P =$ .002), PLT≥220×10^9/L (HR, 2.274; 95% CI, 1.061-4.876; $P =$ .035), PNI≥51.9 (HR, 0.503; 95% CI, 0.265-0.954; $P =$ .035), and GPR≥0.2 (HR, 0.432; 95% CI, 0.204-0.912; $P =$ .028). Other platelet-related indices, such as PDW, PLR, and APPR, were not associated with OS (Table 3).

With the Kaplan–Meier analysis, we further evaluated the role of preoperative platelet-related indices in the OS prediction in the cohort. As shown in Figure 1, the patients with high-PLT, low-GPR, or low-PNI had an unfavorable OS after surgery. Statistical analysis showed a significant difference between the patients stratified by platelet counts (log-rank $P =$ .0004), GPR (log-rank $P =$ .0120), and PNI (log-rank $P =$ .0231), respectively.

Table 3. Univariable and Multivariable Analyses of Prognostic Factors Influencing Overall Survival of Patients after Hepatectomy.

	Univariable			Multivariable		
Variables	HR	95% CI	*P* value	HR	95% CI	*P* value
Baseline Factors						
Age≥58 (years)	1.688	1.075 to 2.651	.023*	2.227	1.347 to 3.850	.002*
Sex						
Male	1	0.149 to 7.700	.946	1	0.019 to 5.006	.409
Female	1.071			0.309		
Alcohol consumption	1.133	0.687 to 1.869	.624	1.728	0.970 to 3.081	.064
Etiology						
Hepatitis	2.158	1.038 to 4.486	.039*	1.529	0.680 to 3.436	.304
Cirrhosis	0.732	0.337 to 1.590	.430	1.470	0.333 to 6.493	.611
Antiviral therapy	0.772	0.433 to 1.377	.381	1.013	0.534 to 1.919	.969
Tumor Markers						
AFP≥100 ug/L	1.393	0.892 to 2.177	.145	1.349	0.797 to 2.284	.265
CA199 ≥ 40 U/mL	1.620	0.966 to 2.718	.068	0.999	0.994 to 1.004	.745
CEA (ug/L)	1.008	0.998 to 1.019	.131	1.014	0.988 to 1.040	.298
Tumor Factors						
Tumor size (cm)	1.030	0.977 to 1.085	.273	1.002	0.932 to 1.077	.951
Tumor size≥5cm	1.343	0.815 to 2.216	.248			
Multiple tumors	0.840	0.454 to 1.554	.578	0.955	0.685 to 1.332	.788
Microvascular invasion	1.332	0.852 to 2.081	.208	1.334	0.787 to 2.259	.284
TNM stage (III + IV)	0.924	0.553 to 1.544	.763	1.061	0.540 to 2.086	.864
Laboratory Results						
WBC (*10^9/L)	1.072	0.953 to 1.205	.248			
LYM (*10^9/L)	0.865	0.583 to 1.283	.470			
PLT≥220 (*10^9/L)	2.433	1.420 to 4.167	.001*	2.274	1.061 to 4.876	.035*
MPV (fL)	0.926	0.744 to 1.153	.494			
PDW≥12.8 (%)	0.623	0.390 to 0.998	.049*	0.526	0.241 to 1.148	.107
Coagulation Indexes						
PT (s)	1.305	0.935 to 1.821	.118			
APTT (s)	1.049	0.971 to 1.134	.224			
TT (s)	0.935	0.750 to 1.165	.550			
FIB (g/L)	1.193	0.912 to 1.561	.197			
Inflammatory indices						
PLR≥116	1.727	1.105 to 2.699	.016*	0.958	0.502 to 1.831	.898
PNI≥51.9	0.543	0.317 to 0.930	.026*	0.503	0.265 to 0.954	.035*
GPR≥0.2	0.502	0.290 to 0.871	.014*	0.432	0.204 to 0.912	.028*
APPR≥0.55	0.627	0.400 to 0.982	.042*	0.757	0.428 to 1.341	.341

Abbreviations: AFP:, α-fetoprotein; APPR: alkaline phosphatase-to-platelet ratio; APTT: activated partial thromboplastin time; CI: confidence interval; CEA: carcinoembryonic antigen; FIB: fibrinogen; GPR: gamma-glutamyl transpeptidase-to-platelet ratio; HR: hazard ratio; LYM: lymphocyte; MPV: mean platelet volume; PLT: platelet; PDW: platelet distribution width; PT: prothrombin time; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; TT: thrombin time ; WBC: white blood cell.
**P* value <.05 was considered significant.

High-PLT and low-GPR are Critical Survival Factors with Propensity Score Matching Analysis

We analyzed the association of the factors with survival with propensity score matching analysis. The main demographic and clinical features were not significantly associated with OS based on propensity score matching (Tables 4 and 5). However, the high-PLT (log-rank $P = .0248$) and low-GPR group (log-rank $P = .0220$) were consistently associated with a more inferior OS (Figure 2).

Discussion

In this study, we evaluated the predictive value of platelet-related measures for HCC patients' survival after surgical resection. The preoperative high-PLT, low-GPR, and low-PNI that were significantly associated with more inferior OS might be independent prognostic factors for predicting survival outcomes of HCC patients.

Platelets are primarily regarded as the essential player in hemostasis and thrombosis. As a versatile factor, platelets also play crucial roles in the inflammatory response and contribute to cancer progression.[15] Platelets could promote tumor cells proliferation and invasion by releasing various soluble factors and allow tumor cells to evade immune surveillance by direct interaction with tumor cells.[16] Furthermore, platelets were also related to the increased risk of cancer metastasis.[17] Based on this, we presumed that platelets could be a potential

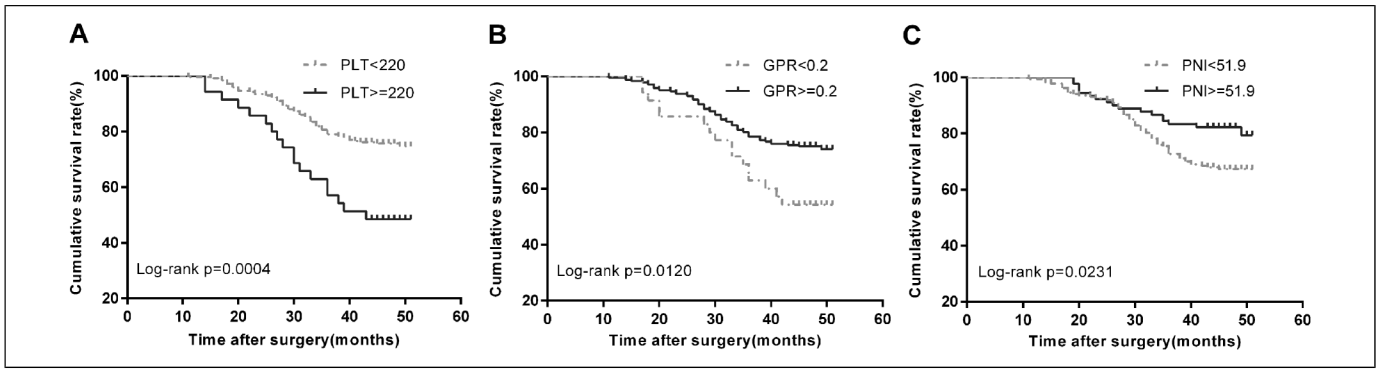

Figure 1. Comparison of overall survival (OS) by Kaplan–Meier curve analysis in the cohort. Patients after surgery were stratified based on (A) platelet count (PLT), (B) gamma-glutamyl transpeptidase-to-platelet ratio (GPR), and (C) prognostic nutritional index (PNI).

Table 4. Comparison of the Main Clinical Characteristics of Patients Classified by PLT Sfter Propensity Score Matching.

	Platelet Count		
Variables	<220 (n = 54)	≥220 (n = 35)	*P* value
Age (years), mean ± *SD*	49.50 ± 11.56	49.69 ± 13.29	.945
Etiology			
Hepatitis	39 (72.2%)	25 (71.4%)	.935
Cirrhosis	50 (92.6%)	31 (88.6%)	.707
Antiviral therapy	13(24.1%)	3 (8.6%)	.063
Tumor Markers			
AFP≥100 ug/L	32 (59.3%)	22 (62.9%)	.734
CA199 ≥ 40 U/mL	6 (11.1%)	7 (20.0%)	.246
CEA [ug/L, median (IQR)]	2.1 [1.4,3.0]	2.2 [1.1, 3.3]	.965
Tumor Factors			
Tumor size (cm), mean ± *SD*	8.64 ± 4.50	10.07 ± 4.44	.147
Multiple tumors	6 (11.1%)	8 (22.9%)	.137
Microvascular invasion	22 (40.7%)	14 (40.0%)	.945
Liver Biochemistry			
ALP [U/L, median (IQR)]	86 [66.0,98.5]	84 [70.5,134.0]	.330
Srum total bilirubin (umol/L), mean ± *SD*	15.35 ± 5.85	14.48 ± 5.61	.492
Serum albumin (g/L), mean ± *SD*	42.61 ± 3.41	41.92 ± 4.12	.397
Inflammatory Indices			
PNI (mean ± *SD*)	50.67 ± 5.62	51.40 ± 5.47	.552
GPR [median (IQR)]	0.44 [0.24, 0.67]	0.39 [0.21, 0.79]	.614

Abbreviations: AFP: α-fetoprotein; ALP: alkaline phosphatase; CEA: carcinoembryonic antigen; GPR: gamma-glutamyl transpeptidase-to-platelet ratio; PNI: prognostic nutritional index.

Table 5. Comparison of the Main Clinical Characteristics of Patients Classified by GPR After Propensity Score Matching

	Gamma-glutamyl transpeptidase-to-platelet ratio		
Variables	<0.2 (n = 35)	≥0.2 (n = 58)	*P* value
Age (years), mean ± *SD*	48.11 ± 13.87	48.6 ± 10.30	.846
Etiology			
Hepatitis	33 (94.3%)	55 (94.8%)	1.000
Cirrhosis	32 (91.4%)	53 (91.4%)	1.000
Antiviral therapy	6 (17.1%)	15 (25.9%)	.330
Tumor Markers			
AFP≥100 ug/L	15 (42.9%)	25 (43.1%)	.925
CA199 ≥ 40 U/mL	1 (2.9%)	9 (15.5%)	.084
CEA [ug/L, median (IQR)]	2.4 [1.5, 3.8]	2.1 [1.6,2.85]	.598
Tumor size (cm), mean ± *SD*	6.47 ± 3.63	6.58 ± 3.33	.885
Liver Biochemistry			
Serum total bilirubin (umol/L), mean ± *SD*	14.28 ± 4.65	13.72 ± 5.78	.636
Serum albumin (g/L), mean ± *SD*	42.43 ± 3.37	41.41 ± 3.45	.170
Laboratory Results			
WBC (–10^9/L), mean ± *SD*	5.82 ± 1.98	5.70 ± 1.64	.752
LYM (×10^9/L), mean ± *SD*	1.69 ± 0.53	1.77 ± 0.70	.572
PLT (×10^9/L), mean ± *SD*	190.70 ± 72.75	171.80 ± 57.78	.169
MPV (fL), mean ± *SD*	11.10 ± 1.04	11.33 ± 0.92	.262
Inflammatory Indices			
PLR [median (IQR)]	108.5 [90.4,133.8]	93.9 [78.8,125.1]	.110
PNI (mean ± *SD*)	49.67 ± 9.43	50.25 ± 5.39	.707

Abbreviations: AFP: α-fetoprotein; CEA: carcinoembryonic antigen; LYM: lymphocyte; MPV: mean platelet volume; PLT: platelet; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; WBC: white blood cell.

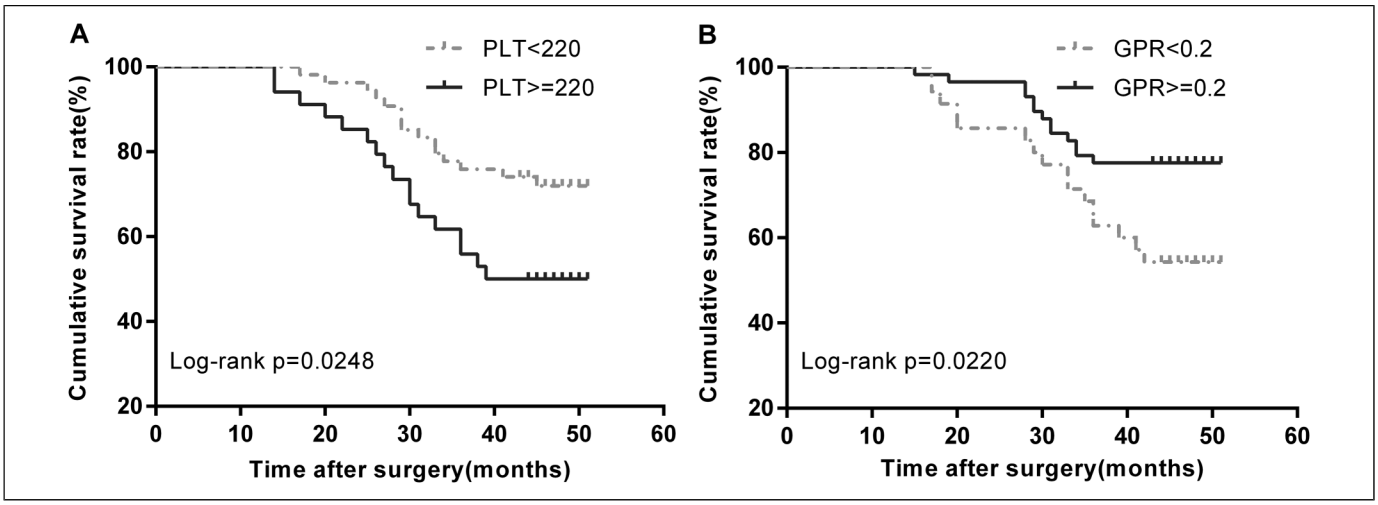

Figure 2. Comparison of overall survival (OS) by Kaplan–Meier curve analysis in the cohort with propensity score matching analysis. Patients after surgery were stratified based on (A) platelet count (PLT) and (B) gamma-glutamyl transpeptidase-to-platelet ratio (GPR).

marker for the progression of HCC. Consistent with most clinical research,[9] our study demonstrated that preoperative high-PLT count (PLT$\geq 200\times10^9$/L) was an independent risk factor for poor prognosis in HCC patients. Propensity score matching analysis, which could avoid potential confounding bias, also indicated that high-PLT counts were associated with adverse survival. Our data further showed PLT count is positively associated with tumor size, which is also in line with previous reports.[18]

We found that platelets were significantly and positively correlated with leucocytes. In tumor sites, platelets could recruit macrophages and neutrophils through multiple mechanisms, such as secretion of chemokine signals (SDF-1, serotonin, PF-4, and β-TG) and the formation of platelet-leukocyte complexes (interaction between platelet P-selectin and leukocyte PSGL-1). The close correlation between platelets and leucocytes showed that platelets were essential for the generation of tumor-associated leucocytes, stimulating platelet–tumor cell aggregation and tumor metastasis.[19] Therefore, these data suggested the potential role of PLT in the tumor microenvironment of HCC. Together, our data not only indicate the clinical significance of PLT in prognosis but also shed light on antiplatelet therapy as a new therapeutic strategy against HCC. Indeed, recent studies have verified the potential role of antiplatelet therapy with aspirin in reducing risks of carcinogenic disease outcomes.[20]

It is not well studied concerning predictive roles of some indices incorporating both blood count and liver function in the survival of HCC patients after hepatic surgery. Our study demonstrated that low-GPR (GPR<0.2) and low-PNI (PNI<51.9) were independent risk factors for predicting poor prognosis of HCC patients. In contrast, the multivariable analysis did not show the significant association of APPR with survival and further study with a bigger cohort needed to clarify its predicatory roles.

Low-GPR was confirmed to be associated with the more inferior OS of patients in our cohort, which is inconsistent with the previous studies.[21] These contradictory data may be explained by the following reasons. First, although the expression of GGT was higher with larger tumors and could promote the development of tumors,[22] patients expressed GGT without a substantial rise, most of whom had liver cirrhosis in the study. It was probably because extensive hepatocyte necrosis, impaired bile, and early-stage of cancer could affect the formation of GGT. Second, high platelet count may play a more important role in our study. Finally, the small sample size, different inclusion criteria, and baseline characteristics of patients, and selection bias may also make a difference.

PNI, as a nutritional and immunological marker, is calculated from two available laboratory parameters (serum albumin level and peripheral lymphocyte count) in routine clinical practice. Our results well supported the prognostic value of PNI in HCC patients. Preoperative low-PNI was associated with poor survival, indicating large tumor size, poor histologic differentiation, and damaged liver function, which is consistent with several previous studies.[23] The predictive role of preoperative low-PNI could be explained by the hypoalbuminemia and lymphocytopenia. Low albumin levels caused by impaired liver function not only significantly correlate with more aggressive tumor parameters,[24] but contribute to the systemic inflammatory response as a harmful acute-phase protein.[25] Lymphocytopenia results in the loss of lymphocytes, which lead to the impairment of host antitumor immunity and further induce cancer relapse and worse prognosis.[26]

Besides, old age was not only risk factors of developing HCC but also the predictors significantly associated with decreased survival in our cohort. Elderly patients could have more comorbidities and lower repair capability of the liver to influence postoperative complications that increased risks of the mortality.[27] The study has several limitations. First, the current study was a single-center preliminary study, and multiple centers are required for further validating our conclusions. Second, the study was a retrospective analysis with a limited number of

patients, and larger-sample data from prospective studies would be better to explain the value of these platelet-related measures in predicting the survival of HCC patients.

Conclusion

In summary, our study demonstrates that high-PLT, low-GPR, and low-PNI are significantly associated with increased risk of death and more inferior OS in HCC patients after hepatectomy. These parameters, simple and easily obtained in routine blood tests, might be effective predictors for evaluating a favorable prognosis in patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval Statement

The study protocol was approved by the Medical Ethics Committee of Huashan Hospital, Fudan University (approval 2013-098).

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: gLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394-424. doi:10.3322/caac.21492
2. Zheng R, Qu C, Zhang S, et al. Liver cancer incidence and mortality in China: temporal trends and projections to 2030. *Chin J Cancer Res.* 2018;30(6):571-579. doi:10.21147/j.issn.1000-9604.2018.06.01
3. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *The Lancet.* 2018;391(10127):1301-1314. doi:10.1016/s0140-6736(18)30010-2
4. Altekruse SF, McGlynn KA, Dickie LA, Kleiner DE. Hepatocellular carcinoma confirmation, treatment, and survival in surveillance, epidemiology, and end results registries, 1992-2008. *Hepatology.* 2012;55(2):476-482. doi:10.1002/hep.24710
5. Fu J, Wang H. Precision diagnosis and treatment of liver cancer in China. *Cancer Lett.* 2018;412:283-288. doi:10.1016/j.canlet.2017.10.008
6. Bihari C, Rastogi A, Shasthry SM, et al. Platelets contribute to growth and metastasis in hepatocellular carcinoma. *APMIS.* 2016;124(9):776-786. doi:10.1111/apm.12574
7. Cheng YQ, Wang K, Zhang XP, et al. Thrombocytopenia: a prognostic factor for hepatocellular carcinoma patients with portal vein tumor thrombus after hepatectomy. *J Gastroenterol Hepatol.* 2019;34(7):1214-1221. doi:10.1111/jgh.14537
8. Zhang AB, Zhang ZH, Zhang J, et al. Lower mean platelet volume is a risk indicator of hepatocellular carcinoma recurrence following liver transplantation. *Hepatobiliary Pancreat Dis Int.* 2019;18-(3):223-227. doi:10.1016/j.hbpd.2019.04.009
9. Scheiner B, Kirstein M, Popp S, et al. Association of platelet count and mean platelet volume with overall survival in patients with cirrhosis and unresectable hepatocellular carcinoma. *Liver Cancer.* 2019;8(3):203-217. doi:10.1159/000489833
10. Zhang Z, Zhang Y, Wang W, et al. Thrombocytopenia and the outcomes of hepatectomy for hepatocellular carcinoma: a meta-analysis. *J Surg Res.* 2017;210:99-107. doi:10.1016/j.jss.2016.11.002
11. Hu Z, Chen H, Chen S, et al. The value of neutrophil to lymphocyte ratio and gamma-glutamyl transpeptidase to platelet ratio in patients with hepatocellular carcinoma. *Medicine (Baltimore).* 2019;98(9):e14749. doi:10.1097/MD.0000000000014749
12. Wang YG, Wang P, Wang B, Fu ZJ, Zhao WJ, Yan SL. Diabetes mellitus and poorer prognosis in hepatocellular carcinoma: a systematic review and meta-analysis. *PLoS One.* 2014;9(5):e95485. doi:10.1371/journal.pone.0095485
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *The Lancet.* 2007;370-(9596):1453-1457. doi:10.1016/s0140-6736(07)61602-x
14. Pang Q, Bi JB, Wang ZX, et al. Simple models based on gamma-glutamyl transpeptidase and platelets for predicting survival in hepatitis B-associated hepatocellular carcinoma. *Onco Targets Ther.* 2016;9:2099-2109. doi:10.2147/OTT.S101465
15. Franco AT, Corken A, Ware J. Platelets at the interface of thrombosis, inflammation, and cancer. *Blood.* 2015;126(5):582-588. doi:10.1182/blood-2014-08-531582
16. Pavlovic N, Rani B, Gerwins P, Heindryckx F. Platelets as Key factors in hepatocellular carcinoma. *Cancers (Basel).* 2019;11-(7):1022. doi:10.3390/cancers11071022
17. Lee CH, Lin YJ, Lin CC, et al. Pretreatment platelet count early predicts extrahepatic metastasis of human hepatoma. *Liver Int.* 2015;35(10):2327-2336. doi:10.1111/liv.12817
18. Carr BI, Guerra V, Pancoska P. Thrombocytopenia in relation to tumor size in patients with hepatocellular carcinoma. *Oncology.* 2012;83(6):339-345. doi:10.1159/000342431
19. Kim J, Bae JS. Tumor-Associated macrophages and neutrophils in tumor microenvironment. *Mediators Inflamm.* 2016;2016:6058147. doi:10.1155/2016/6058147
20. Lee M, Chung GE, Lee JH, et al. Antiplatelet therapy and the risk of hepatocellular carcinoma in chronic hepatitis B patients on antiviral treatment. *Hepatology.* 2017;66(5):1556-1569. doi:10.1002/hep.29318
21. Ke MY, Zhang M, Su Q, et al. Gamma-glutamyl transpeptidase to platelet ratio predicts short-term outcomes in hepatocellular carcinoma patients undergoing minor liver resection. *J Surg Res.* 2018;231:403-410. doi:10.1016/j.jss.2018.05.049

22. Hanigan MH. Gamma-glutamyl transpeptidase: redox regulation and drug resistance. *Adv Cancer Res.* 2014;122:103-141. doi:10.1016/B978-0-12-420117-0.00003-7
23. Fan X, Chen G, Li Y, et al. The preoperative prognostic nutritional Index in hepatocellular carcinoma after curative hepatectomy: a retrospective cohort study and meta-analysis. *J Invest Surg.* 2021;34(8):826-833. doi:10.1080/08941939.2019.1698679
24. Carr BI, Guerra V. Serum albumin levels in relation to tumor parameters in hepatocellular carcinoma patients. *Int J Biol Markers.* 2017;32(4):e391-e396. doi:10.5301/ijbm.5000300
25. McMillan DC. An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer. *Proc Nutr Soc.* 2008;67(3):257-262. doi:10.1017/S0029665108007131
26. Man YG, Stojadinovic A, Mason J, et al. Tumor-infiltrating immune cells promoting tumor invasion and metastasis: existing theories. *J Cancer.* 2013;4(1):84-95. doi:10.7150/jca.5482
27. Faber W, Stockmann M, Schirmer C, et al. Significant impact of patient age on outcome after liver resection for HCC in cirrhosis. *Eur J Surg Oncol.* 2014;40(2):208-213. doi:10.1016/j.ejso.2013.10.018